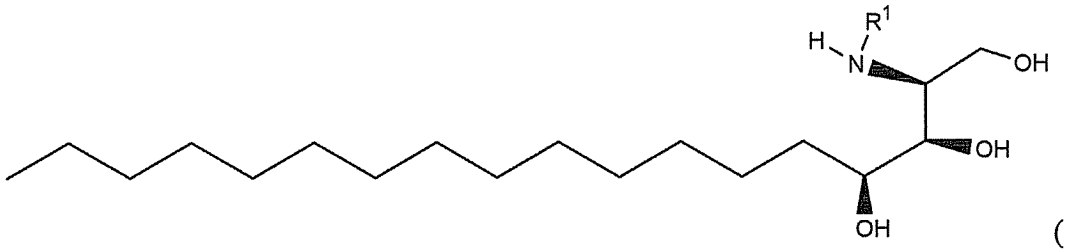
REMARKS

Claims 1-6 are pending in the present Application. Claims 2-3 and 5-6 have been canceled, Claims 1 and 4 have been amended, Claim 13 has been added and Claims 7-12 have been withdrawn, leaving Claims 1, 4 and 13 for consideration upon entry of the present Amendment.

Reconsideration and allowance of the claims are respectfully requested in view of the above amendments and the following remarks.

Amended Claims

Claims 1 and 4 have been amended to claim a composition for cancer treatment comprising a pharmaceutically acceptable carrier and a compound represented by formula 1 or a pharmaceutically acceptable carrier and a pharmaceutically acceptable salt of the compound represented by formula 1. The compound of formula 1 is shown below:



(1)

Support for the amendment to Claims 1 an 4 can be found at least on page 5, lines 32 – 33 of the specification as originally filed where it is stated that "[T]he composition of the present invention may comprise a pharmaceutically acceptable carrier." No new matter has been introduced by this amendment.

New Claims

A new Claim 13 has been added. New Claim 13 is directed to a composition for cancer treatment comprising a pharmaceutically acceptable carrier and a compound obtained from an acylation of an amino group on phytosphingosine or a pharmaceutically acceptable carrier and a compound obtained from an acylation of an amino group on phytosphingosine derivative wherein the cancer is selected from the group consisting of lung cancer, uterine cancer, breast cancer and blood cell cancer; and wherein the phytosphingosine derivative is

one having an alkylcarbonyl group that is selected from the group consisting of a propanoyl group, a butanoyl group, a pentanoyl group, a hexanoyl group, a heptanoyl group, an octanoyl group, a nonanoyl group, a decanoyl group, an undecanoyl group, or a dodecanoyl group.

Support for Claim 13 can be found at least on page 5 lines 21 – 22 where it is stated that the phytosphingosine derivative can be easily obtained by acylation of an amino group on phytosphingosine. Further support for Claim 13 can be found at least on page 5, line 17 where it states that the phytosphingosine derivative has an alkylcarbonyl group. Additional support for Claim 13 can be found at least on page 5, lines 13 – 16.

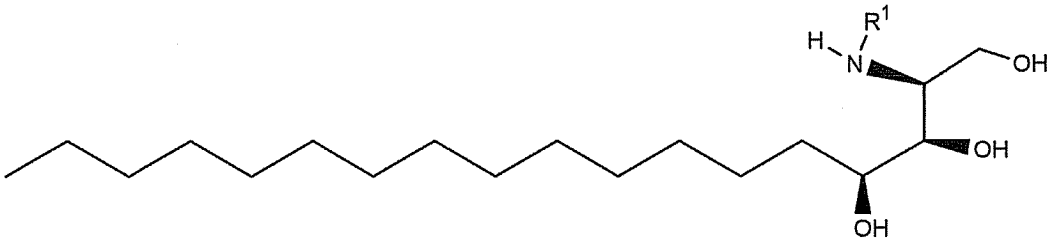
Claim Rejections Under 35 U.S.C. § 102(b)

Claims 1 and 4 stand rejected under 35 U.S.C. § 102(b), as allegedly being anticipated by WO 99/58542 to Weber et al., (hereinafter Weber) (Office Action dated 09/30/2008, page 4) The Applicants respectfully disagree.

In making the rejection, the Examiner stated that "Weber teaches a composition of N-acetylated amino alcohols wherein the compound is N-octanoyl and N-hexanoyl phytosphingosine. See pages 14 and 15. (Office Action dated 09/30/2008, page 4) The Applicants respectfully disagree.

To anticipate a claim, a reference must disclose each and every element of the claim. *Lewmar Marine v. Varient Inc.*, 3 U.S.P.Q.2d 1766 (Fed. Cir. 1987).

As currently amended, the claimed invention is generally directed to a composition for cancer treatment comprising a pharmaceutically acceptable carrier and a compound represented by formula 1 or a pharmaceutically acceptable carrier and a pharmaceutically acceptable salt of the compound represented by formula 1, wherein the cancer is selected from the group consisting of lung cancer, uterine cancer, breast cancer and blood cell cancer:



(1)

wherein, R^1 is propanoyl group, butanoyl group, pentanoyl group, hexanoyl group, heptanoyl group, octanoyl group, nonanoyl group, decanoyl group, undecanoyl group, or dodecanoyl group.

Claim 4 is directed to the composition of Claim 1, which can have a radiosensitizing effect.

Claim 13 is directed to a composition for cancer treatment comprising a pharmaceutically acceptable carrier and a compound obtained from an acylation of an amino group on phytosphingosine or a pharmaceutically acceptable carrier and a compound obtained from an acylation of an amino group on phytosphingosine derivative wherein the cancer is selected from the group consisting of lung cancer, uterine cancer, breast cancer and blood cell cancer; and wherein the phytosphingosine derivative is one having an alkylcarbonyl group that is selected from the group consisting of a propanoyl group, a butanoyl group, a pentanoyl group, a hexanoyl group, a heptanoyl group, an octanoyl group, a nonanoyl group, a decanoyl group, an undecanoyl group, or a dodecanoyl group.

Weber discloses a process for N-acetylation of amino alcohols employing an organic acid in the form of an acid halogenide. (see abstract) Weber discloses that the amino alcohol is a sphingoid base having the formula:

$$R'—A—CH(OR''')—CH_3(NH_2)-CH_2—OR''$$

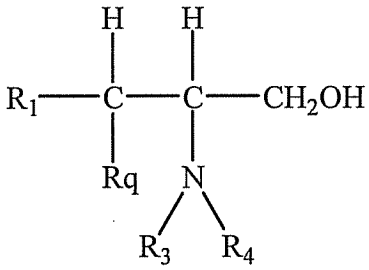
where R′ is a straight chain or branched alkyl group having 10 to 22 carbon atoms, R′′ is hydrogen and R′′′ is hydrogen. (see page 5) In its examples, Weber teaches that the amino alcohol comprising the sphingoid base can be reacted with hexanoyl chloride to produce N-hexanoyl-phytosphingosine (see Example 6) or reacted with octanoyl chloride to produce N-octanoyl-phytosphingosine (see Example 5).

Weber however, does not teach the use of a pharmaceutically acceptable carrier in conjunction with the compound of formula (1) or the use of a pharmaceutically acceptable carrier in conjunction with a pharmaceutically acceptable salt of the compound of formula (1). In a similar vein, Weber does not teach all elements of Claim 4, for the aforementioned reasons. Similarly, with respect to Claim 13, Weber does not teach a composition for cancer treatment comprising a pharmaceutically acceptable carrier and a compound obtained from an acylation of an amino group on phytosphingosine.

For this reason at least, Weber cannot anticipate Claim 1, Claim 4 or Claim 13. The Applicants therefore respectfully request a withdrawal of the anticipation rejection over Weber and an allowance of the claims.

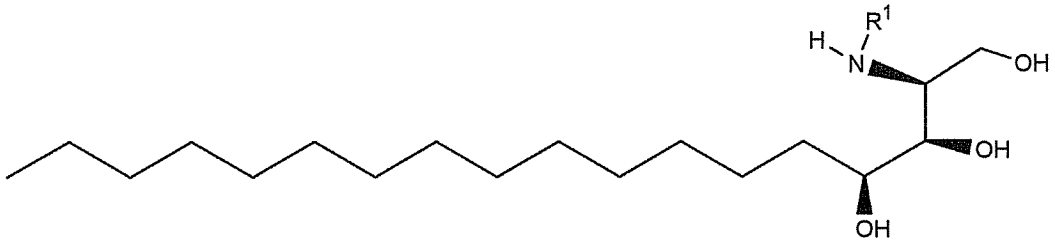
Claim 1 stands rejected under 35 U.S.C. § 102(b), as allegedly being anticipated by WO 92/03129 to Hannun et al., (hereinafter Hannun) (Office Action dated 09/30/2008, page 5) The Applicants respectfully disagree.

In making the rejection, the Examiner has stated that

> Hannun et al. disclose a ceramide compound of structural formula (I)
>
> 
>
> (I)
>
> where R1 is C_1-C_{20} and R_3 is H and R_4 is COR_5, wherein R_5 is C_1-C_{20} alkynyl, alkyl (see page 4, lines 6 – 20). The said composition is used for the treatment of cancer wherein the cancer is leukemia (a blood cancer) as required by instant claims 1 and 4, see page 9, lines 29 – 35, page 10, lines 1 – 37.

(Office Action dated 09/30/2008, page 5)

As alleged by the Examiner, Hannun teaches the ceramide compound of structural fomula (I) shown immediately above. Hannun however, does not teach a compound having the instant Formula (1)



as claimed in Claim 1 and 4. The compound of the instant Formula (1) does not fall within the generic scope of Hannun's Formula I. The instant Formula (1) requires the presence of

three hydroxyl groups while Hannun's Formula I allows for only two hydroxyl groups (not including OH substitution on the amide alkyl chain). In order for the instant Formula 1 to be anticipated by Hannun, R_1 of Hannun would have to allow for substitution on the C_1-C_{20} alkyl group by hydroxyl, which it does not. (see page 7, line 16 and see also page 7, line 29 to page 8, line 1)

In addition, Hannun, like Weber does not teach the use of a pharmaceutically acceptable carrier in conjunction with the compound of formula (1) or the use of a pharmaceutically acceptable carrier in conjunction with a pharmaceutically acceptable salt of the compound of formula (1). For this reason also, Hannun cannot anticipate Claim 1, Claim 4 or Claim 13.

The instant Claim 1 and Claim 4 are not, therefore anticipated by Hannun. The Applicants therefore respectfully request a withdrawal of the anticipation rejection over Hannun and an allowance of the claims.

Claim Rejections Under 35 U.S.C. § 103(a)

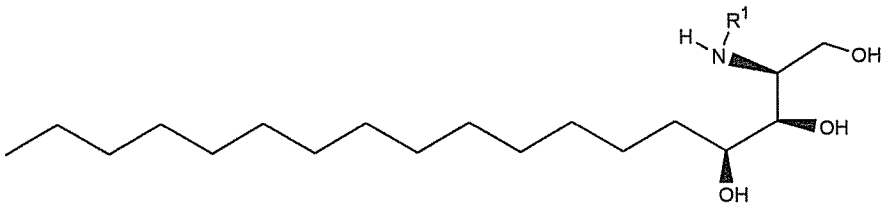
Claim 4 stands rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Weber and Hannun in view of WO 92/03129 in view of Haimovitz-Friedman et al. (J. Exp. Med. 180, 1994, 525-535) (hereinafter "Friedman"). (Office Action dated 09/30/2008, page 5) Applicants respectfully traverse this rejection.

In making the rejection, the Examiner contends that "Friedman allegedly teaches that ionizing radiation like TNFα induces rapid sphingo-myelin hydrolysis to ceramide and that apoptosis in bovine aortic endothelial cells and that elevation of ceramide with an exogenous ceramide analogue was sufficient for induction of the apoptosis signal. The Examiner further contends that Friedman allegedly teaches that ionization increased the ceramide level and that apoptosis is the mechanism of radiation induced cell death in hematopoitic (blood) cells." (Office Action dated 09/30/2008, page 6)

The Examiner concludes it would have been obvious to enhance the apoptotic effect of the lipid by exposing cells (blood) to radiation and administration of the ceramide of Weber because Friedman teaches that the ceramides activity are increased when exposed to ionization. (Office Action dated 09/30/2008, page 6)

The Examiner further concludes that it would have been obvious to employ the compounds of Weber and utilize them for the enhancement of a radio sensitizing effect because Friedman shows that ionization enhances ceramides apoptosis ability. Since Weber allegedly teaches the compounds are ceramides, the Examiner states one would expect to see the same result. (Office Action dated 09/30/2008, page 6)

Claim 4 is directed to a composition for the enhancement of radiosensitizing effect comprising a pharmaceutically acceptable carrier and a compound represented by formula 1 or a pharmaceutically acceptable carrier and a pharmaceutically acceptable salt of the compound represented by the formula 1:

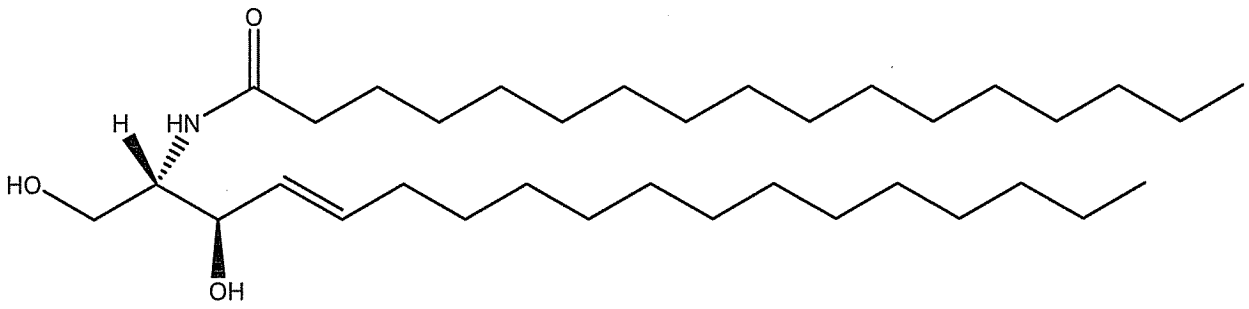


(1)

wherein, R^1 is propanoyl group, butanoyl group, pentanoyl group, hexanoyl group, heptanoyl group, octanoyl group, nonanoyl group, decanoyl group, undecanoyl group, or dodecanoyl group.

For an obviousness rejection to be proper, the Examiner must meet the burden of establishing that all elements of the invention are disclosed in the prior art. *In re Fine*, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). The Supreme Court has recently reaffirmed the principle that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the art.... This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *KSR Int'l. Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). The Court further stated that "[r]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *Id.* (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

Ceramides have the general structural formula (II) (please see Appendix A, enclosed herewith):



(II)

As can be seen from the general structural formula (II), ceramides consist of a long-chain or sphingoid base linked to a fatty acid via an amide bond. As can be seen in Appendix B enclosed herewith, fatty acids are carboxylic acids with long hydrocarbon chains. The hydrocarbon chain length may vary from 10-30 carbons (most usual is 12-18).

Weber therefore does not disclose ceramides. In Example 5, the fatty acid disclosed by Weber has only 8 carbon atoms, while in the Example 6, the fatty acid has only 6 carbon atoms. The amino acids acetylated by Weber thus do not result in the formation of ceramides. More specifically, Weber does not teach the use of a pharmaceutically accepted carrier in conjunction with a compound having the instant formula 1 or with a salt of the instant compound of the formula 1.

As noted above, Hannun does not disclose compounds of the instant formula 1. Hannun, lik Weber, does not teach the use of a pharmaceutically accepted carrier in conjunction with a compound having the instant formula 1 or with a salt of the instant compound of the formula 1.

Friedman teaches that tumor necrosis factor α (TNF-α) receptor interaction initiates sphingomyelin hydrolysis to ceramide by a sphingomyelinase and that ionizing radiation induces rapid sphingomylin hydrolysis to ceramide and apoptosis. (see Summary) Friedman also states that elevation of ceramide with exogenous ceramide analogs (i.e., compounds capable of metabolism to a ceramide) was sufficient to induce apoptosis. (see page 525 last 4 lines) There is no suggestion in Weber, Hannun or Friedman alone or in combination to use compounds that cannot be metabolized into a ceramide. The compounds according to the instant Formula 1 are not ceramides nor can they be metabolically converted to ceramides.

In addition, neither Weber, Hannun nor Friedman teach the use of pharmaceutically acceptable carrier in conjunction with the compound of Formula (1) or the pharmaceutically acceptable carrier in conjunction with a derivative of the compound of Formula (1). They additionally do not teach the use of a pharmaceutically acceptable carrier with a pharmaceutically acceptable carrier and a compound obtained from an acylation of an amino group on phytosphingosine.

Additionally, there is no suggestion on motivation in any of the cited references to use the compounds according to the instant Formula 1 in a composition for the enhancement of a radio sensitizing effect.

In addition, there is no motivation to combine Weber with Hannun. As noted above, Weber teaches amino acid acetylating of phytosphingosine that does not result in the formation of ceramides. The structures disclosed by Weber however, have three hydroxyl moieties. The structures disclosed by Hannun, on the other hand, have only two hydroxyl moieties. Weber thus teaches away from Hannun. In addition, Hannun, in teaching only two hydroxyl moieties teaches away from the claimed invention.

One of ordinary skill in the art noting these two disparities would not have sought to combine these references in the manner made by the Examiner.

In summary, neither Weber, Hannun nor Friedman teach all elements of the claimed invention. There is further no motivation to combine Weber with Hannun since they teach away from each other. For these reasons at least, the Applicants believe that the Examiner has not made a prima facie case of obviousness over Weber and Hannun in view of Friedman. The Applicants respectfully request a withdrawal of the obviousness rejection of Claim 4 and an allowance of the claim.

Conclusion

It is believed that the foregoing amendments and remarks fully comply with the Office Action and that the claims herein should now be allowable to Applicants. Accordingly, reconsideration and allowance are requested.

If there are any additional charges with respect to this Amendment or otherwise, please charge them to Deposit Account No. 06-1130.

Respectfully submitted,

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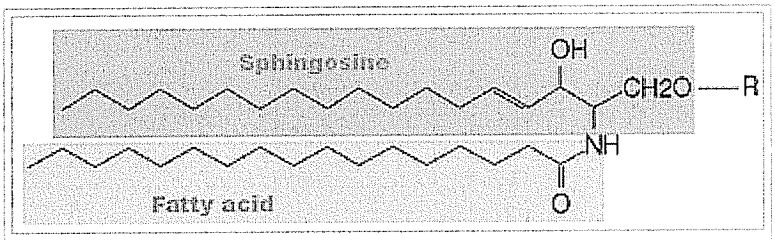
APPENDIX A

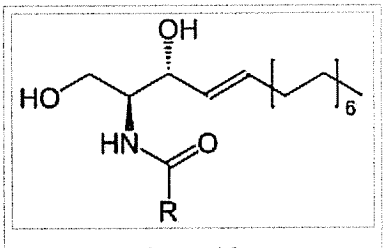
Ceramide

From Wikipedia, the free encyclopedia



General chemical structure of sphingolipids. Different substituents (R) give: **H - ceramide**, phosphocholine - sphingomyelin, sugar(s) - glycosphingolipid(s).

Ceramides are a family of lipid molecules. A ceramide is composed of sphingosine and a fatty acid. Ceramides are found in high concentrations within the cell membrane of cells. They are one of the component lipids that make up sphingomyelin, one of the major lipids in the lipid bilayer. For years, it was assumed that ceramides and other sphingolipids found in the bilayer cell membrane were purely structural elements. This is now known to be not completely true. Perhaps one of the most fascinating aspects of ceramide is that it can act as a signaling molecule. The most well-known functions of ceramides as cellular signals include regulating the differentiation, proliferation, programmed cell death (PCD), and apoptosis (Type I PCD) of cells.



Ceramide

Contents

Pathways for ceramide synthesis

There are three major pathways of ceramide generation. The sphingomyelinase pathway uses an enzyme to breakdown sphingomyelin in the cell membrane and release ceramide. The de novo pathway creates ceramide from less complex molecules. Ceramide generation can also occur through breakdown of complex sphingolipids that are ultimately broken down into sphingosine, which is then reused by reacylation to form ceramide. This latter pathway is termed the Salvage pathway.

Sphingomyelin Hydrolysis

Hydrolysis of sphingomyelin is catalyzed by the enzyme sphingomyelinase. Because sphingomyelin is one of the four common phospholipids found in the plasma membrane of cells, the implications of this

method of generating ceramide is that the cellular membrane is the target of extracellular signals leading to programmed cell death. There has been research suggesting that when ionizing radiation causes apoptosis in some cells, the radiation leads to the activation of sphingomyelinase in the cell membrane and ultimately, to ceramide generation.[1]

De novo

De novo synthesis of ceramide begins with the condensation of palmitate and serine to form 3-keto-dihydrosphingosine. This reaction is catalyzed by the enzyme serine palmitoyl transferase and is the rate-limiting step of the pathway. In turn, 3-keto-dihydrosphingosine is reduced to dihydrosphingosine, which is then followed by acylation by the enzyme (dihydro)ceramide synthase to produce dihydroceramide. The final reaction to produce ceramide is catalyzed by dihydroceramide desaturase. De novo synthesis of ceramide occurs in the endoplasmic reticulum. Ceramide is subsequently transported to the Golgi. In the Golgi apparatus, ceramide can be further metabolized to other sphingolipids, such as sphingomyelin and the glycosphingolipids.[2]

The Salvage Pathway

Constitutive degradation of sphingolipids and glycosphingolipids takes place in the acidic subcellular compartments, the late endosomes and the lysosomes. In case of glycosphingolipids, exohydrolases, acting at acidic pH optima, cause the stepwise release of monosaccharide units from the end of the oligosaccharide chains one after the other leading to the generation of ceramide whereas sphingomyelin is converted to ceramide by acid sphingomyelinase. Ceramide can be further hydrolyzed by acid ceramidase to form sphingosine and a free fatty acid, both of which are able to leave the lysosome in contrast to ceramide. The long-chain sphingoid bases released from the lysosome may then re-enter pathways for synthesis of ceramide and/or sphingosine-1-phosphate. The salvage pathway re-utilizes long-chain sphingoid bases to form ceramide through the action of ceramide synthase [20]. Thus, ceramide synthase family members probably trap free sphingosine released from the lysosome at the surface of the endoplasmic reticulum or in endoplasmic reticulum-associated membranes. It should also be noted that the salvage pathway has been estimated to contribute from 50% to 90% of sphingolipid biosynthesis [3]

Physiological Roles of Ceramide

As a bioactive lipid, ceramide has been implicated in a variety of physiological functions including apoptosis, cell growth arrest, differentiation, cell senescence, cell migration and adhesion. [2] Roles for ceramide and its downstream metabolites have also been suggested in a number of pathological states including cancer, neurodegeneration, diabetes, microbial pathogenesis, obesity, and inflammation. [4]

Apoptosis

One of the most studied roles of ceramide pertains to its function as a proapoptotic molecule. Apoptosis, a form of programmed cell death, is essential for the maintenace of normal cellular homeostasis and is an important physiological response to many forms of cellular stress. Ceramide accumulation has been found following treatment of cells with a number of apoptotic agents including ionizing radiation [1][5], UV light [6], TNF-alpha [7], and chemotherapeutic agents. This suggests a role for ceramide in the biological responses of all these agents. Because of its apoptosis-inducing effects in cancer cells,

ceramide has been termed the "tumor suppressor lipid" . Several studies have attempted to define further the specific role of ceramide in the events of cell death and some evidence suggests ceramide functions upstream of the mitochondria in inducing apoptosis. However, owing to the conflicting and variable nature of studies into the role of ceramide in apoptosis, the mechanism by which this lipid regulates apoptosis remains elusive. [8].

Substances known to induce ceramide generation

- TNF-alpha
- Fas ligand
- Endotoxin
- Chemotherapeutic agents
- 1,25 dihydroxy vitamin D
- gamma interferon
- heat
- ionizing radiation [1][9]
- Ceramidase Inhibitors

It is interesting to note that the substances that can cause ceramide to be generated tend to be stress signals that can cause the cells to go into programmed cell death. Ceramide thus acts as an intermediary signal that connects the external signal to the internal metabolism of the cells.

Mechanism by which ceramide signalling occurs

Currently, the means by which ceramide acts as a signaling molecule are not clear.

One hypothesis is that ceramide generated in the plasma membrane stabilizes smaller lipid platforms known as lipid rafts, allowing them to serve as platforms for signalling molecules. Moreover, as rafts can cross the entire lipid bilayer, they can serve as the link between signals outside of the cell to signals to be generated within the cell.

Ceramide has also been shown to form organized large channels traversing the mitochondrial outer membrane. This leads to the egress of proteins from the intermembrane space. [10][11][12]

References

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11. ^ Stiban J, Fistere D, Colombini M (2006). "Dihydroceramide hinders ceramide channel formation: Implications on apoptosis". *Apoptosis* **11** (5): 773–80. doi:10.1007/s10495-006-5882-8. PMID 16532372.
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External links

- MeSH *Ceramides*

Fatty Acids

Table of Fatty Acids

Acid Name	Structure	Melt Point	Graphic	Chime
SATURATED				
Lauric	$CH_3(CH_2)_{10}COOH$	+44	Graphic	Chime
Palmitic	$CH_3(CH_2)_{14}COOH$	+63	.	Chime
Stearic	$CH_3(CH_2)_{16}COOH$	+70	Graphic	Chime
UNSATURATED				
Oleic	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$	+16	Graphic	Chime
Linoleic	$CH_3(CH_2)_4(CH{=}CHCH_2)_2(CH_2)_6COOH$	-5	Graphic	Chime
Linolenic	$CH_3CH_2(CH{=}CHCH_2)_3(CH_2)_6COOH$	-11		Chime
Arachi-donic	$CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2COOH$	-50	Graphic	Chime

Fatty acids are merely carboxylic acids with long hydrocarbon chains. The hydrocarbon chain length may vary from 10-30 carbons (most usual is 12-18). The non-polar hydrocarbon alkane chain is an important counter balance to the polar acid functional group. In acids with only a few carbons, the acid functional group dominates and gives the whole molecule a polar character. However, in fatty acids, the non-polar hydrocarbon chain gives the molecule a non- polar character.

Quiz: Which acid (short chain or fatty) would most likely be soluble in water?	Answer
... in hexane?	Answer

Table of Fatty Acids on the left:

The most common fatty acids are listed. Note that there are two groups of fatty acids--saturated and unsaturated. Recall that the term **unsaturated** refers to the presence of one or more double bonds between carbons as in alkenes. A **saturated fatty acid** has all bonding positions between carbons occupied by hydrogens.

The melting points for the saturated fatty acids follow the boiling point principle observed previously. Melting point principle: **as the molecular weight increases, the melting point increases.** This observed in the series lauric (C12), palmitic (C16), stearic (C18).

Room temperature is 25°C, Lauric acid which melts at 44° is still a solid, while arachidonic acid has long since melted at -50°, so it is a liquid at room temperature.

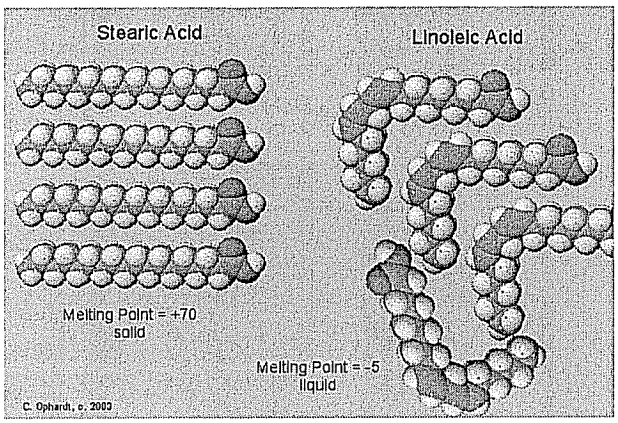
Melting Points of Saturated vs. Unsaturated Fatty Acids:

Note that as a group, the **unsaturated fatty acids have lower melting points than the saturated fatty acids**.

The reason for this phenomenon can be found by a careful consideration of molecular geometries. The tetrahedral bond angles on carbon results in a molecular geometry for saturated fatty acids that is relatively linear although with zigzags. See graphic on the left.

This molecular structure allows many fatty acid molecules to be rather closely "stacked" together. As a result, close intermolecular interactions result in relatively high melting points.

On the other hand, the introduction of one or more double



Click for larger image

bonds in the hydrocarbon chain in unsaturated fatty acids results in one or more "bends" in the molecule. The geometry of the double bond is almost always a cis configuration in natural fatty acids. These molecules do not "stack" very well. The intermolecular interactions are much weaker than saturated molecules. As a result, the melting points are much lower for unsaturated fatty acids.

Quiz: If room tempereature is 25°, which of the following fatty acids is a solid or liquid at room tmeperature.	
Palmitic	Answer
Oleic	Answer

Percent Fatty Acid Present in Triglycerides

Fat or Oil	Saturated		Unsaturated		
	Palmitic	Stearic	Oleic	Linoleic	Other
Animal Origin					
Butter	29	9	27	4	31
Lard	30	18	41	6	5
Beef	32	25	38	3	2
Vegatable Origin					
Corn oil	10	4	34	48	4
Soybean	7	3	25	56	9
Peanut	7	5	60	21	7
Olive	6	4	83	7	-

Saturated vs. Unsaturated Fatty Acids in Fats and Oils:

Examine the table on the left, if you want the most unsaturated fatty acids in your diet, which is the most healthy, which fat or oil should you use the most? Answer = olive oil.

Which fat or oil contains the most saturated fatty acids? Answer = beef fat.

General Principle:

Vegetable oils contain more unsaturated fatty acids.

Animal fats contain more saturated fats.

Quiz on Fatty Acids:

Write down your answers.
Then check the answers from the drop down menu.

Which fat or oil contains the most double bonds?	Answer
Which fats or oils are likely to be liquids at room temperature?	Answer
Which fats or oils have the least amount of unsaturated fatty acids?	Answer